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ARTICLE

Diagnosis and management of antiphospholipid syndrome

SUMMARY

Antiphospholipid syndrome is an autoimmune disease characterised by thrombotic and/or obstetric manifestations with persistent antiphospholipid antibodies.

Diagnosis involves confirming the persistence of antiphospholipid antibodies in symptomatic patients, using validated classification criteria as a guide. The likelihood of obtaining false-positive or false-negative test results in certain settings, and the lack of standardisation between laboratory methods, are important considerations.

Patients who have had thrombotic manifestations require lifelong anticoagulation from the first thrombotic event, typically with warfarin. Patients with a history of thrombotic and/or obstetric manifestations who become pregnant should receive low-molecular-weight heparin and low-dose aspirin during pregnancy and postpartum.

Testing asymptomatic people is not recommended, except in the context of systemic lupus erythematosus. Management of asymptomatic people with persistent antiphospholipid antibodies depends on their individual antibody profile and risk factors.

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Introduction

Antiphospholipid syndrome (APS) is a rare, multisystem autoimmune disorder that is characterised by thrombotic and/or obstetric manifestations with persistent antiphospholipid antibodies. It has an estimated prevalence of 17 to 50 per 100,000 population.[1,2]

APS may occur as a primary autoimmune disorder (53 to 59% of people with APS),[3,4] or as a secondary condition in association with an autoimmune connective tissue disease, most commonly systemic lupus erythematosus (SLE), but also systemic sclerosis, primary Sjögren syndrome and rheumatoid arthritis.[3] Patients with APS usually require tertiary care as part of a multidisciplinary team to optimise patient management.

This article aims to provide an overview of APS diagnosis, including common clinical manifestations, the role and limitations of antiphospholipid antibody testing, and the updated APS classification criteria. Management of clinical manifestations and asymptomatic people with persistent antiphospholipid antibodies is also discussed.

Diagnosis

Patients are usually investigated for APS following the occurrence of a suggestive clinical manifestation. Confirming the diagnosis involves testing for the persistence of antiphospholipid antibodies and interpreting these results in the context of the patient's clinical presentation, using validated classification criteria as a guide.

Clinical manifestations

Thrombotic manifestations

Venous thromboembolism resulting in deep vein thrombosis is the most common presenting manifestation of APS, affecting approximately 32% of people with APS. Pulmonary embolism occurs in approximately 9% of people with APS.[5]

Arterial thromboembolism secondary to APS most commonly presents as stroke, representing around 13% of first presentations of APS. Transient ischaemic attack is also a common first presentation (approximately 7%).[5] APS may also be associated with rare stroke syndromes, such as cerebral venous sinus thrombosis. Other possible arterial thromboembolic manifestations are acute myocardial infarction, acute lower limb ischaemia, avascular necrosis of bone, mesenteric infarction and renal vessel occlusion.[6]

Microvascular thrombosis secondary to APS can result in acute and chronic antiphospholipid antibody nephropathy, adrenal and pulmonary haemorrhage, and myocardial disease. Cutaneous manifestations including lower limb ulceration, subungual splinter haemorrhages and livedo racemosa (a violaceous branching and non-continuous discolouration of the skin) can also occur.[7,8]

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Catastrophic APS is a rare, life-threatening presentation in people with thrombotic manifestations of APS, whereby microvascular or small-vessel thrombosis leads to concurrent multiorgan dysfunction (e.g. acute kidney injury, mesenteric ischaemia, myocardial infarction). It should be suspected in patients with thrombosis with 2 or more organs concurrently involved; involvement of 3 organs concurrently is diagnostic. Catastrophic APS most commonly occurs when there has been an interruption to or a change in long-term anticoagulation in patients with known APS (e.g. in the perioperative period; in concomitant inflammatory states such as infection, surgery or malignancy).[4]

Obstetric manifestations

Early and late obstetric manifestations, such as fetal loss, pre-eclampsia or placental insufficiency, are possible sequelae of APS. In a study among pregnant women with APS-related complications, the most common complication in the mother was pre-eclampsia (9.5%). Early fetal loss occurred in approximately 35% of pregnancies and late fetal loss in 17% of pregnancies. Approximately 11% of live births were premature.[5] There is also an increased risk of maternal venous thromboembolism in APS.

Other clinical manifestations

Valvular heart disease with cardiac valve thickening (with occasional significant valve masses) resulting in regurgitation (Libman–Sacks endocarditis) is the most common cardiac manifestation.[9]

Mild to moderately severe thrombocytopenia is the most common haematological manifestation of APS. An uncommon manifestation is haemolytic anaemia, which can occur either secondary to thrombotic microangiopathy or with an autoimmune association.[5]

Antiphospholipid antibodies

As thrombotic and obstetric manifestations are not unique to APS, reliable confirmation of persistent antiphospholipid antibodies is crucial for accurate diagnosis. Antiphospholipid antibodies encompass a heterogeneous group of immunoglobulins that bind phospholipids, phospholipid-binding plasma proteins and phospholipid–protein complexes at cell surfaces. They activate the endothelium, platelets and leucocytes, which promotes thrombotic and inflammatory complications.[10-12]

The 3 commonly tested antiphospholipid antibodies are anticardiolipin, anti-beta2-glycoprotein I and lupus anticoagulant (Table 1). Of all 3 antibodies, a persistently positive lupus anticoagulant carries the highest risk for developing future clinical manifestations.[19,20] With regard to anticardiolipin and anti-beta2-glycoprotein I, the immunoglobulin G (IgG) isotype confers a higher risk than the immunoglobulin M (IgM) isotype.[14]

Some people may test positive for more than one antibody. Individuals with double antibody positivity are considered to have a high-risk antibody profile. Triple-positive APS, defined as the persistence of all 3 antibodies, confers the highest risk for development of thrombotic and obstetric manifestations.[21,22]

Indications for testing

Testing for antiphospholipid antibodies should be limited to patients in whom there is a high clinical suspicion of APS. Testing may be warranted in younger individuals (especially those under 50 years) who present with unexplained venous thromboembolism or arterial thrombosis (e.g. ischaemic stroke, transient ischaemic attack, acute myocardial infarction). Testing may also be indicated in those with adverse pregnancy outcomes such as recurrent early fetal losses, or one or more fetal deaths later in pregnancy.[23]

Screening for antiphospholipid antibodies in asymptomatic individuals is not recommended, including in those with a family history of APS, or who are pregnant or planning pregnancy. This is to avoid incidental findings which can lead to patient anxiety and unnecessary treatment.[23] The exception to this is people with SLE. Antiphospholipid antibodies are present in 20 to 30% of patients with SLE and may lead to increased risk of thrombotic or obstetric manifestations. Antibody testing in patients with SLE can be considered, especially in those who are pregnant or planning pregnancy, and in the context of other factors that increase the risk of thrombosis such as commencing estrogen-containing contraception.[3,24]

Potential pitfalls of testing

When ordering antiphospholipid antibody tests or interpreting test results, there are potential pitfalls that should be considered (Table 2).

Classification criteria

Classification criteria for APS were developed to identify homogeneous patient cohorts for clinical studies; however, they can be helpful in practice to guide diagnosis. Classification criteria outlining clinical manifestations and laboratory criteria were initially proposed in 1998, then updated in 2006.[30] The American College of Rheumatology and European Alliance of Associations for Rheumatology published a further update in 2023 to capture advancements in the understanding of APS and address limitations of the 2006 criteria, such as the lack of evidence-based definitions for individual manifestations.[7]

The 2023 classification criteria apply weighting to individual criteria and have a higher specificity (99%) but lower sensitivity (86%) compared with the 2006 criteria. According to the 2023 criteria, patients can be classified as having APS if they score at least 3 points from the clinical criteria and 3 points from the laboratory criteria, with at least one clinical criterion and one laboratory criterion present within 3 years of each other (Table 3).[7]

The 2023 classification criteria specify anticardiolipin and anti-beta2-glycoprotein I antibody titres as measured by enzyme-linked immunosorbent assay; however, in practice, many laboratories in Australia employ other analytical methods with differing cut-off values. Given this, there are challenges in directly applying the laboratory classification criteria to all test results and results may be incomparable between laboratories.

Management

Patients with thrombotic manifestations

In patients with persistent antiphospholipid antibodies, the first thrombotic episode would confirm the diagnosis of APS. These patients should be initially treated with standard therapeutic anticoagulation (i.e. subcutaneous low-molecular-weight heparin or intravenous unfractionated heparin).[31]

Secondary prophylaxis with warfarin is required lifelong from the first thrombotic episode, with a target INR of 2 to 3. Some patients may require a higher target INR (e.g. recurrent venous thromboembolism despite an INR of 2 to 3).[31]

Direct-acting oral anticoagulants (DOACs) (e.g. rivaroxaban, apixaban) are not appropriate for secondary prophylaxis as the rate of recurrent thromboembolism with DOACs is significantly higher than with warfarin in patients with APS.[32,33] However, DOACs may be considered in patients who are unable to achieve target INR, unable to adhere to regular INR monitoring, or who have contraindications to warfarin.[31] In patients with a low risk of APS (e.g. low-titre antibody positivity with single thrombotic event in the context of provoking factors), it is unclear if warfarin remains superior to DOACs.

If subsequent thrombotic episodes occur despite therapeutic anticoagulation with warfarin, the addition of an antiplatelet drug such as low-dose aspirin or dipyridamole should be considered.[34]

For management of a patient with thrombotic manifestations who becomes pregnant, see below.

Patients with obstetric manifestations

People with APS who plan to conceive are recommended to receive preconception assessment, including counselling on the increased risk of adverse

Table 1 Description of commonly tested antiphospholipid antibodies

Antiphospholipid antibody	Description
Anticardiolipin antibodies (IgG or IgM)	These antibodies target cardiolipin, an anionic phospholipid component of the inner mitochondrial membrane. Nonpathological anticardiolipin antibodies (associated with a lower risk of thrombosis) can be transiently produced at low titres in response to infection, some autoimmune diseases and malignancy.[13] IgG antibodies are more strongly correlated with thrombosis than IgM antibodies.[14]
Anti-beta2-glycoprotein I antibodies (IgG or IgM)	These antibodies target beta2-glycoprotein I, a phospholipid-binding protein that acts as a naturally occurring inhibitor of platelet aggregation in plasma and inhibits contact activation of the coagulation cascade.[15] IgG antibodies have been strongly associated with thrombotic events; IgM antibodies have less clinical relevance.[14,16,17]
Lupus anticoagulant	Lupus anticoagulant is not a single antibody itself, but refers to a collection of antibodies that interfere with phospholipid-dependent coagulation.[18] A persistently positive lupus anticoagulant carries the highest risk for developing future clinical manifestations compared with anticardiolipin and anti-beta2-glycoprotein I antibodies.[19,20]

IgG = immunoglobulin G; IgM = immunoglobulin M

Table 2 Potential pitfalls of antiphospholipid antibody testing and practical considerations

Potential pitfall of testing	Practical considerations
Non-persistence of antiphospholipid antibodies	Antiphospholipid antibodies may be transiently present in individuals without APS.[25] To reduce the likelihood of a false-positive result, a follow-up test should be performed at least 12 weeks after the initial test to confirm persistence of antibody positivity.
False-negative and false-positive results	False-positive results can occur because of transient anticardiolipin antibodies during infection, some autoimmune diseases and malignancy.[26] Immunoglobulin infusions, plasmapheresis or antibody-depleting therapy can interfere with antibody titres.[23] Vitamin K antagonists (e.g. warfarin) have been associated with both false-positive and false-negative results for lupus anticoagulant.[23] Direct-acting oral anticoagulants can interfere with lupus anticoagulant testing and produce false-positive results, even at low doses.[23]
Lack of standardisation of antibody tests	Methods for detection of antiphospholipid antibodies (in particular anticardiolipin and anti-beta2-glycoprotein I antibodies), diagnostic cut-offs and normal reference ranges differ between laboratories. Therefore, it can be difficult to apply titre cut-offs specified in classification criteria and inaccurate to compare results from different laboratories.[27-29]

Table 3 Summary of 2023 classification criteria for antiphospholipid syndrome[7] [NB1]

Clinical criteria	Points
Macrovascular manifestations [NB2]	
Venous thromboembolism:	
• with high-risk venous thromboembolism profile	1
• without high-risk venous thromboembolism profile	3
Arterial thrombosis:	
• with high-risk cardiovascular disease profile	2
• without high-risk cardiovascular disease profile	4
Microvascular manifestations	
One or more of the following **suspected**:	2
• livedo racemosa (examination)	
• livedoid vasculopathy lesions (examination)	
• acute or chronic antiphospholipid antibody nephropathy (examination or laboratory results)	
• pulmonary haemorrhage (symptoms or imaging)	
One or more of the following **established**:	5
• livedoid vasculopathy (pathology)	
• acute or chronic antiphospholipid antibody nephropathy (pathology)	
• pulmonary haemorrhage (bronchoalveolar lavage or pathology)	
• myocardial disease (imaging or pathology)	
• adrenal haemorrhage (imaging or pathology)	
Obstetric manifestations	
• 3 or more consecutive prefetal (less than 10 weeks) and/or early (from 10 weeks to 15 weeks and 6 days) fetal deaths	1
• fetal death (from 16 weeks to 33 weeks and 6 days) without pre-eclampsia or placental insufficiency with severe features	1
• pre-eclampsia **or** placental insufficiency with severe features (less than 34 weeks) with or without fetal death	3
• pre-eclampsia **and** placental insufficiency with severe features (less than 34 weeks) with or without fetal death	4
Other clinical manifestations	
• cardiac valve thickening	2
• cardiac valve vegetation	4
• thrombocytopenia	2
Laboratory criteria [NB3][NB4]	
• positive lupus anticoagulant (single, one time)	1
• positive lupus anticoagulant (persistent)	5
• moderate or high positive IgM antibodies to anticardiolipin and/or anti-beta2-glycoprotein I (persistent)	1
• moderate positive IgG antibodies to anticardiolipin and/or anti-beta2-glycoprotein I (persistent)	4
• high positive IgG antibodies to anticardiolipin **or** anti-beta2-glycoprotein I (persistent)	5
• high positive IgG antibodies to anticardiolipin **and** anti-beta2-glycoprotein I (persistent)	7

IgG = immunoglobulin G; IgM = immunoglobulin M

NB1: A person is classified as having antiphospholipid syndrome if they score at least 3 points from the clinical criteria and at least 3 points from the laboratory criteria, with at least one clinical criterion and one laboratory criterion present within 3 years of each other.

NB2: Determination of the risk of venous thromboembolism and cardiovascular disease is based on general population guidelines – refer to full classification criteria.[7]

NB3: Persistence of antiphospholipid antibodies is defined as positive laboratory results on 2 occasions, at least 12 weeks apart.

NB4: The classification criteria specify antibody titres as measured by coagulation-based functional assay (for lupus anticoagulant) and enzyme-linked immunosorbent assay (for anticardiolipin and anti-beta2-glycoprotein I antibodies).

Adapted from Barbhaiya M, Zuily S, Naden R, Hendry A, Manneville F, Amigo MC, et al. The 2023 ACR/EULAR Antiphospholipid Syndrome Classification Criteria. Arthritis Rheumatol 2023;75:1687-702. https://doi.org/10.1002/art.42624

maternal and fetal outcomes and how these risks may impact the perceived benefits of having a child. After pregnancy is confirmed, these patients should be referred to an obstetrician or obstetric medicine physician as their situation would be considered a high-risk pregnancy. All patients with SLE, especially those with persistent antiphospholipid antibodies, should also be encouraged to discuss plans for conception with their treating specialist.

If a patient with a history of **obstetric** manifestations (but no history of thrombotic manifestations) becomes pregnant, both **prophylactic-dose** low-molecular-weight heparin and low-dose aspirin are recommended for the duration of the pregnancy and postpartum for 6 to 12 weeks.[31,35] As low-molecular-weight heparin is associated with an increased risk of osteoporosis, it is important to minimise the treatment duration of this drug to a maximum of 12 weeks. Patients should be checked for, and advised on, appropriate dietary intake of calcium and vitamin D. If there are recurrent obstetric complications despite treatment, increasing the heparin dose to a therapeutic dose or adding hydroxychloroquine may be considered.[31]

If a patient with a history of **thrombotic** manifestations (but no history of obstetric manifestations) becomes pregnant, **therapeutic-dose** low-molecular-weight heparin and low-dose aspirin are recommended for the duration of the pregnancy and for 6 to 12 weeks postpartum.[35] Patients previously on warfarin should be switched to low-molecular-weight heparin because of the risk of birth defects with warfarin.[31]

Long-term thromboprophylaxis for patients with a history of obstetric manifestations who are not pregnant or hoping to conceive is not recommended; however, low-dose aspirin may be considered short term in high-risk situations (e.g. long-haul flights, surgery).

People with a history of obstetric manifestations who develop a thrombotic episode should be managed as per patients with APS-associated thrombosis (i.e. lifelong secondary prophylaxis with warfarin).[31]

Catastrophic antiphospholipid syndrome

If catastrophic APS is suspected, the patient should be immediately referred to a hospital for assessment and management. Initial treatment involves anticoagulation and high-dose corticosteroids, and is often followed by plasma exchange and/or rituximab or cyclophosphamide.[4]

Asymptomatic people with persistent antiphospholipid antibodies

Investigating for antiphospholipid antibodies is not recommended in asymptomatic individuals, except in patients with SLE. If an asymptomatic person is antibody positive on the initial test, a follow-up test is recommended to confirm antibody persistence.

Asymptomatic people with persistent antiphospholipid antibodies do not have a diagnosis of APS; however, management may be required based on an assessment of the individual's risk of developing future clinical manifestations. Their risk is informed by their individual antibody profile, coexistence of other systemic autoimmune diseases such as SLE, and the presence of thromboembolic and cardiovascular risk factors.[31] All people with persistent antiphospholipid antibodies should be educated on the relevance of antiphospholipid antibodies and supported to address their modifiable thromboembolic and cardiovascular risk factors, such as smoking and obesity.[31]

There is uncertainty surrounding the role of primary prophylaxis with aspirin for asymptomatic people with persistent antiphospholipid antibodies.[36,37] The benefits and harms of using low-dose aspirin should be considered on an individual basis. Thromboprophylaxis with low-dose aspirin may be considered in asymptomatic people with a high-risk antibody profile (e.g. persistent lupus anticoagulant, triple antibody positivity) who are trying to conceive and have strong unmodifiable risk factors for thrombosis.[31,33] Short-term thromboprophylaxis (e.g. with low-molecular-weight heparin) may also be considered in situations with a high risk of developing venous thromboembolism (e.g. peripartum period, surgery, flights).

In patients with SLE and a high-risk antibody profile, prophylactic low-dose aspirin is recommended.[31] Hydroxychloroquine is the mainstay treatment for people with SLE and may have additional benefits for people with SLE who have persistent antiphospholipid antibodies.[3]

All patients with SLE who are hoping to conceive should receive preconception counselling. In asymptomatic pregnant women with persistent antibodies (with or without SLE), prophylactic low-dose aspirin before 16 weeks gestation has been recommended with careful monitoring of the fetus and the mother.[31,35]

Conclusion

Testing for antiphospholipid antibodies should only be initiated in patients in whom there is a high clinical suspicion of APS or with SLE. The detection of persistent antiphospholipid antibodies is key to the diagnosis and risk stratification of patients with APS. However, there are challenges with the interpretation of test results.

Patients with thrombotic manifestations of APS should be initially treated with therapeutic heparin, followed by warfarin for long-term secondary prophylaxis.

Pregnant patients with APS require low-dose aspirin and low-molecular-weight heparin at either a therapeutic or prophylactic dose, depending on prior manifestations, during pregnancy and postpartum.

Asymptomatic people with persistent antiphospholipid antibodies do not have a clinical diagnosis of APS. The decision to initiate thromboprophylaxis in this group is based on their individual antiphospholipid antibody profile and other risk factors. ≺

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